APPENDIX 9

absent in our patient, is a flat or raised, yellowish glial tumor or "phakoma" on the retina or optic nerve head.

An hypertrophied extremity that has not been heretofore described in the skin lends support to an opinion expressed by a number of writers that tuberous sclerosis is allied to a few rare developmental disorders in which angiomatosis is the underlying factor.

That tuberous sclerosis is a disorder of development is generally accepted. It is primarily a disturbance of embryogenesis involving more particularly the ectoderm and to a less extent the mesoderm. The former is reflected in the skin and nervous system manifestations, the latter in the propensity for embryonic tumor formation in the kidney, heart and other viscera. As an example of maldevelopment and malformation of ectodermal tissue it is considered closely related to von Recklinghausen's neurofibromatosis. Indeed there have been cases reported in which an individual has shown characteristics of both diseases.

The pathology of Bourneville's disease is further corroboration of its developmental nature. The brain surface is studded with flat, pale, firm nodules that distort the gyri. On the floor of the lateral ventricles many subependymal nodules resembling candle-gutterings are seen. These sometimes obstruct the ventricular system and give rise to an increase in intracranial pressure. Microscopically there is distortion and disturbance of the normal six layers of the cortex with a diminution in the normal number of nerve cells. The characteristic feature is the presence of grotesquely formed, huge nerve cells, and large bizarre malformed astrocytes. The nodules in the ventricles are composed chiefly of spongioblasts. Here and there calcium is deposited in the maldeveloped tissue and may be demonstrated radiographically. This marked disorganization of the brain adequately explains the mental deficiency and epilepsy that form such a prominent part of the symptomatology.

Unfortunately there is no specific treatment for this condition. Anticonvulsant medication tends to reduce the number of seizures. Most of these individuals gravitate to institutions for the feeble-minded and epileptic where in time they succumb to status epilepticus, bronchopneumonia, tuberculosis or some other debilitating disease.

The New Synthetic Estrogen, Stilbestrol

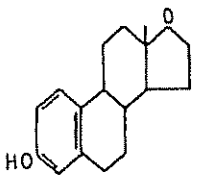
By K. K. Chen, M. D.

Throughout the centuries the English people have made notable contributions to medicine along the line of therapeutics. We can readily recall the introduction of smallpox vaccination by Edward Jenner, marking the beginning of preventive medicine: the cautious use of digitalis by William Withering for the treatment of dropsy and cardiac failures; and the popularization of antiseptics by Lord Lister, leading to modern aseptic surgery. During the last few years, by far the most important contribution by the British has been the discovery of sulfapyridine for the treatment of lobar pneumonia by the chemists Ewins and Phillips and the pathologist Whitby.

Perhaps of equal significance is the synthesis of the new estrogenic compound stilbestrol by Dodds of London. Chemically, stilbestrol may be called 4 : 4'-dihydroxy-α : β-diethylstilbene. It is highly estrogenic—more active than the natural product estrone. The discovery of stilbestrol has several points of unusual interest. In the first place, it is one of few examples that a man-made chemical is actually more potent than the natural substance of the same class. Secondly, its ease and low cost of production are very striking. Thirdly, it represents a totally different type of compound from a chemical point of view, as shown below, and yet it has all the characteristic effects of natural estrogens.

Fourthly, stilbestrol is effective by mouth in very small doses, much more so than natural estrogens. Fifthly, it spoils our conception of

specificity of hormone action. Physiologists and endocrinologists have been teaching that in case of hypofunction of endocrine glands, replacement therapy by the hormones of the same glands must be employed. Thus, in diabetes mellitus. Insulin made from the pig or beef pancreas must be injected to make up the deficiency from which the patient is suffering. No other substance can accomplish the purpose.



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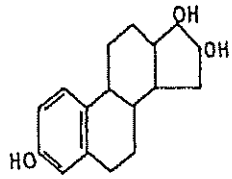

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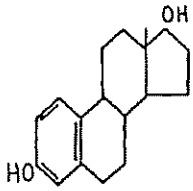

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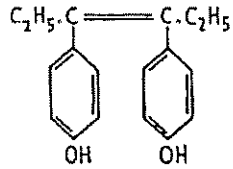

STILBESTROL

This is the specificity of action. Here in stilbestrol we have a new compound of different chemical structure which is entirely alien to the body but it produces responses exactly the same as the natural estrogenic hormones will do.

1. *Potency.* This is a very important point to know, so that proper doses for humans may be adopted. Dodds showed in spayed rats that stilbestrol is 2½ times as potent as estrone. Subsequent workers either confirm Dodds' results or give figures for stilbestrol as large as 5 times that of estrone. In our laboratory, we employed immature female rats, and used premature vaginal opening and increase in uterine weight as the criteria. Our data indicate that by subcutaneous injection stilbestrol is 25 times as strong as estrone, and by mouth, it is 11 times as potent as estrone. These results are summarized in Table 1.

Table 1—Comparison of Estrogenic Activity of Stilbestrol and Estrone in Immature Rats

Route of Administration	Drug	Number of Rats Used	Median Estrous Dose ± Standard Error	Ratio of Estrone: Stilbestrol
Subcutaneous	Stilbestrol	60	γ per rat 0.131 ± 0.011	1:25
	Estrone	60	3.649 ± 0.417	
Oral	Stilbestrol	133	0.403 ± 0.022	1:11
	Estrone	60	4.629 ± 0.704	

2. *Toxicity.* Single, small doses of both stilbestrol and estrone were repeated daily for a period of 8 weeks. The growth curves of these animals are practically the same as that of the control. With large doses of both stilbestrol and estrone there was definite inhibition of growth. At the end of the experiment, all the animals were s microscopically served except and the female hypertrophy of gland, but atro shown in Tabl necrotic. Cats a bestrol and est after a few do was apparent th vomiting.

3. *Clinical R* reports have be the continent. some are perh this reason that by summarized gations were n peace of mind.

Table 2—Prolonged Oral Administration of Stilbestrol and Estrone in Rats

Medication	Number of Animals	Daily Dose per Rat	Duration of Experiment	Average Change in Weight ± Standard Error				
				Ovaries	Uterus	Adrenals	Thymus	Pituitary Gland
			Weeks	mg.	mg.	mg.	mg.	mg.
Stilbestrol	10	0.4γ	8	38.54 ± 3.17	235.9 ± 39.1	38.64 ± 1.79	333.2 ± 17.1	7.96 ± 0.34
Estrone	8	3.5γ	8	39.22 ± 5.17	293.4 ± 56.0	37.29 ± 2.77	294.6 ± 29.3	7.95 ± 0.78
None	10	0	8	40.26 ± 2.14	385.4 ± 58.9	38.15 ± 1.78	325.2 ± 17.0	8.54 ± 0.41
Stilbestrol	10	5-10 mg.	12			49.58 ± 4.30	52.8 ± 3.5	15.34 ± 1.18
Estrone	10	1 mg.	12			38.48 ± 1.58	100.9 ± 11.5	7.26 ± 0.40
None	10	0	12			26.05 ± 1.58	134.0 ± 10.2	6.01 ± 0.42

Author

Collins, Weed, W and Lock

Huberman and C

Diddle and Keett

Davis

Weed, Weinstein, et al.

Payne and Muckl

Walter, Salmon a Geist

Shorr, Robinson Papanicolaou

Buxton and Engl

Sevringhaus

Russ and Collins

MacBryde, Freen Castrodale

Lewis

Karnaky

Finkler and Mark

Allan

Table 3—Clinical Reports on Stilbestrol

Authors	Reference	Number of Cases	Type of Cases	Improvement	Side Reactions
				Percent	Percent
Collins, Weed, Weinstein and Lock	Am. J. Obs. & Gyn. *39*:117, 1939	50	Menopause, hypoestrinism, senile vaginitis	100	60
Huberman and Colmer	Ibid. *39*:783, 1940	77	Menopause	90	36
Diddle and Keettel	Ibid. *39*:791, 1940	10	Senile vaginitis, Menopause	100	80
Davis	Ibid. *39*:985, 1940	100	Menopause, amenorrhea	93	20
Weed, Weinstein, Collins et al.	Ibid. *39*:1047, 1940	57	Menopause, hypoestrinism	95	?
Payne and Muckle	Ibid. *40*:135, 1940	68	Menopause	86	10
Walter, Salmon and Geist	Ibid. *40*:243, 1940	45	Menopause	89	64
Shorr, Robinson and Papanicolaou	J.A.M.A. *113*:2312 1939	44	Menopause, amenorrhea	90	80
Buxton and Engle	Ibid. *113*:2318, 1939	17	Menopause, senile vaginitis, amenorrhea	88	29
Sevringhaus	Ibid. *114*:685, 1940	17	Menopause	100	?
Russ and Collins	Ibid. *114*:2446, 1940	25	Vulvovaginitis	100	?
MacBryde, Freeman and Castrodale	Ibid. *115*:440, 1940	56	Menopause, hypo-ovarianism	92	16
Lewis	Yale, J. Biol. Med. *12*:235, 1939	18	Menopause, amenorrhea	83	11
Karnaky	South. Med. J. *32*:818, 1939	189	Menopause, amenorrhea	100	?
Finkler and Morks	N. J. Med. J. *37*:99, 1940	4	Senile vaginitis	100	?
Allan	Lahey Clin. Bull. *1*:14, 1940	32	Menopause	94	30

animals were sacrificed and studied grossly and microscopically. No visceral changes were observed except those of the endocrine organs and the female genital tract. There was definite hypertrophy of uterus, adrenals, and pituitary gland, but atrophy of ovaries and thymus, as shown in Table 2. In rabbits, the uterus was necrotic. Cats are more susceptible to both stilbestrol and estrone. They lost their appetite after a few doses, and became moribund. It was apparent that stilbestrol caused nausea and vomiting.

3. *Clinical Results.* No less than 77 clinical reports have been published in England and on the continent. A few of them are excellent, but some are perhaps overenthusiastic. It is for this reason that the American literature is hereby summarized in Table 3, because the investigations were made with better facilities, more peace of mind, and less bias, realizing of course that the priority of the work must go primarily to the British scientists.

Stilbestrol may be used in cases where natural estrogenic products are indicated. They comprise climacteric symptoms (physiological, surgical, or radiological), primary amenorrhea, prepuberal vulvovaginitis, and senile vaginitis. These reports constitute a good sample of geographical distribution.

Clinical improvements may be recorded objectively by vaginal smears, endometrial biopsies, withdrawal bleeding, and breast changes; and subjectively by relief of symptoms such as hot flushes, headaches, etc. It is almost unanimously agreed that stilbestrol can reproduce all the effects of natural estrogenic substances in men.

The most annoying feature in the clinical use of stilbestrol has been the occurrence of side reactions. They are nausea, vomiting, loss of

appetite, abdominal distress, diarrhea, lassitude, vertigo, skin rash, and in a single instance psychosis. By far the most common symptoms are nausea and vomiting; the others are rare. There is a marked discrepancy concerning the frequency of the untoward effects. Some clinicians observed them occasionally but were unable to control them by the reduction of doses. On the other hand, some gynecologists recorded unfavorable reactions in as high as 80 percent of their cases. The question of dosage must play an important role in the production of side reactions. One must bear in mind that, first, stilbestrol has an inherent property of causing nausea and vomiting; and secondly, it is 25 times as potent as estrone by injection, and 11 times as potent by mouth as revealed in our own experiments. It appears that in the majority of cases the doses used were excessively large and that the incidence of nausea and vomiting might have been lower if smaller amounts were employed. Based on our own data, a quantity of 0.1 mgm. of stilbestrol has a potency of 2500 international units by injection, and 1100 international units by mouth. Uniformly negative results were obtained in blood chemistry, renal and hepatic function tests, and other clinical studies, following the administration of stilbestrol. In other words, the new synthetic drug in therapeutic doses does not cause damage to the organs of the body. The occasional appearance of nausea and vomiting is comparable to that under sulfapyridine therapy.

Summary

The new synthetic estrogen, stilbestrol, is highly effective by mouth, economic in production, and has a relatively low toxicity. In men it can substitute natural estrogenic products. In conservative doses, side effects, chiefly nausea and vomiting, may be reduced to a minimum.

The Effects of Obstetrical Anaesthesias and Analgesias on the Newborn

By Ottis N. Olvey
Class of 1941

Ideal obstetrical anaesthesia and analgesia must be without harm to the newborn child, relieve the mother's labor pains, and not interfere with the natural forces of labor.

Through many channels, women have learned that pain in childbirth is no more necessary than it is in the various surgical procedures. As a result, they are demanding painless labor and should have it. But, at the same time, the fact must not be lost sight of, that in giving adequate relief to the mother serious damage or death, immediately or later, may be inflicted upon the newborn child. Many feel, and an equal number do not, that the drugs used are so often the cause of anoxemia, cerebral anoxia delayed cry, listlessness in the newborn, asphyxia livida and pallida, spasticity, convulsions, mental retardation, and neonatal death.

The first toxic effect of the barbiturates, scopolamine, paraldehyde, etc., is to depress the respiratory center. When this reaches sufficient intensity, a state of asphyxia occurs and breathing ceases. This is called cerebral anoxia and apnea. If this is complete for even ten minutes, it may lead to irreparable damage to the child's nervous system. Histologically, in a case of anoxia, certain areas of the brain show edema, cuff hemorrhage, and pyknosis of ganglion cells. It has been shown that those who have apnea and die, with no analgesics having been given to the mother, have the same brain lesions and damage as the much higher percentage of those who have apnea and die with analgesics having been given.

Schreiber and Gates[2] have shown in a series of three hundred cases diagnosed as "brain injuries" and seen because of spasticity, convulsions, and mental retardation that no matter

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